## REMARKS

Claims 17-26 are currently pending.

The claims are amended to more particularly state the subject matter which Applicants regard as their invention. None of the amendments constitute new matter.

The claims are rejected as anticipated, and/or obvious. For reasons discussed below, it is requested that all the rejections be removed and that the claims be allowed to issue.

### 1. The Claims Are Not Anticipated By Knighton

Claims 17-21 are rejected under 35 U.S.C. §102(b) as being anticipated by United States Patent No. 5,165,938 by Knighton ("Knighton"). The Examiner contends that the compositions of Knighton contain " 'microparticles' derived from platelet-rich plasma after activation with collagen and centrifugation" which "are mixed with microcrystalline collagens and frozen." The Examiner notes that the drug composition of Knighton (i) is made under sterile conditions and from material (blood) "collected from normal patients that are not diagnosed with viral diseases and thus, virus depleted or virus free;" (ii) contains growth factors such as PDAF and PDGF; (iii) contains fibrinogen and thrombin because they are "inherent components of a product derived from platelet rich plasma;" (iv) contains organic polymers such as proteins and/or glycoproteins; (v) contains inorganic compounds or inorganic salts; and (vi) can be used "in conjunction with either biodegradable dressings or with some implantable devices.".

The Examiner, in the Response to Arguments section of the pending Official Action, states:

> applicants appear to argue that the claimed invention is directed to microparticles separated "from" supernatant (thrombocyte supernatant) unlike the cited product that is present "in" supernatant (response page 5-7). This argument neither has persuasive grounds nor is true. first, the claimed invention does not recite what is

> discarded and what is retained. Further, the cited reference clearly teaches that the activated platelet rich plasma is subjected to a removal of platelets and fibrin by centrifugation and that the resulting supernatant is a source of molecules or "microparticles" such as PDGF and PDAF that are released from the activated platelets . . . The cited patent clearly teaches molecular weight of "microparticles" such as PDGF and PDAF and, thus, they are separated "from" supernatant as argued. The cited final product such as the PDGF and PDAF-containing supernatant has the wound healing effects as the claimed product.

As a preliminary matter, Applicants wish to address two points raised in this rejection.

First, the Examiner makes the statement "the resulting supernatant is a source of molecules or 'microparticles' such as PDGF and PDAF" which indicates that the definition being applied to "microparticles" is very broad, and includes organic molecules such as the growth factors PDGF and PDAF. This definition of "microparticles" is overly broad and incorrect in view of the specification, which states, at paragraph 2,

> If stimulated appropriately, eukaryotic cells are able to release parts of their plasma membrane into the extracellular space. Those cell fragments contain cytoplasmic moeties and are referred to as microparticles. The formation of such microparticles could be verified in monocytes, lymphocytes, endothelial cells, granulocytes and thrombocytes. In the case of thrombocytes, stimulation with collagen thrombin, Ca.sup.2+-ionophore A23187, and protein C5b-9 of the complement system results in exocytosis of such cellular elements (Tans G., Blood 1991; Sims P J., J Biol Chem 1988). In addition to the above-mentioned substances, which cause a modification of the intracellular calcium concentration, the formation of thrombocytic microparticles has been ascribed to protein phosphorylations, the translocation of phospholipids, changes in the cytoskeleton, and shear forces.

Second, in the Response to Arguments, the Examiner stated that Applicants' prior argumentation "neither has persuasive grounds nor is true." While it may indeed have been the case that the Examiner was not persuaded by Applicants' argumentation, Applicants take serious exception to the Examiner's statement that their argument was "not true," and, in the event that this case goes to Appeal, wish to make of record that the only basis offered by the Examiner for

her statement were differences in interpretation, rather than any false statement made by Applicants.

Turning to the merits of the rejection, Applicants assert that the claims are not anticipated by Knighton for at least the following reason.

As recognized by the Examiner, based on the "Response to Arguments" cited above, Knighton uses the *supernatant* when platelet-rich plasma is separated into a platelet and fibrin-containing "pellet" and a supernatant which contains growth factors.

As previously explained, the present claims provide that microparticles are collected from this supernatant, and it is these microparticles, separated from the liquid medium into which they had been released, which are comprised in the therapeutic composition. Unlike Knighton, the supernatant is not used.

The Examiner has contended that the claim language prior to the amendments made herein would encompass separating the microparticles from the supernatant and then mixing them back together again. Applicants do not believe that this is a reasonable interpretation of the claims, because it would make the limitation requiring separation meaningless. Nevertheless, Applicants have inserted the limitation, "such that the microparticles in the composition are separated from the liquid medium into which they had been released," thereby removing, beyond any doubt, the possibility that the supernatant is added back to the composition.

Because anticipation requires that the cited art teach each and every element of the claims, this substantial difference- that Knighton uses a platelet supernatant and the claimed invention does not - establishes the novelty of the claims over Knighton, such that the rejection should be withdrawn.

**2. The Claims Are Not Anticipated By Chao**

Claims 17-21 are rejected under 35 U.S.C. §102(b) as anticipated by United States Patent No. 5,185,160 by Chao ("Chao"). The Examiner contends that Chao teaches a pharmaceutical composition comprising viral-inactivated platelet membrane microparticle fractions "made by activation of platelets by repeated freezing and thawing" and then "separated or collected by centrifugation." Exner et al., 2003, Blood Coag. Fibrinol. 14:773-779 ("Exner") is cited to "evidence the inherent fact that freezing-thawing activates platelets."

In the "Response to Arguments" section of the pending Official Action, the Examiner disputes Applicants contention that Chao's microparticles are not the same as those of the claims because they were activated in a different way. The Examiner states that the "inherent fact that platelets are activated by freezing-thawing is evidenced by Exner et al." and concludes that "there is no reason to believe that the 'microparticles of US 5,185,160 (Chao) might be different from the claimed 'microparticles.' "

In response, Applicants assert, first, that the contention that the microparticles of the invention and those of Chao are the same is without merit. The Examiner is applying an incorrect standard for inherency. The legal standard requires that the feature is *"necessarily present"* (see Applicants' citation to *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) in the previously submitted response), rather than that there is no reason to believe they are different. Moreover, the Examiner has simply presented reasons that she does not agree with the cited journal articles offered by Applicants in support of their position, rather than advancing any comparable evidence to support the contention of "sameness" upon which the rejection is based. Applicants assert that Lindemann et

al., 2001, J. Cell Biol. 154:485-490 and Alberio et al., 1998, Br. J. Hematol. 102:1212-1218, provided as Exhibits A and B in the previously submitted response, provide sound reasons that show that the microparticles of the presently claimed invention and those of Chao are not necessarily the same, such that anticipation on inherency grounds is improper. In further support of Applicants' position, the Examiner's attention is invited to column 2 lines 46-54, which states that the vesicles used by Chao, while they may be produced from platelet membrane, may also be prepared from other cell membranes. In contrast, the generation of microparticles according to the invention depends upon the use of platelets and their activation by a specific set of agents.

Moreover, the Examiner does not at all address the other half of Applicants' argument, namely that Chao (like Knighton) uses microparticles in the context of a supernatant but the claimed invention does not. Chao states (at column 2 line 66 through column 3 line 9):

> The ghost platelets then are separated from the lysate and are suspended in a solution to form a suspension. Then the suspension containing the ghost platelets is heated to at least 60°C for at least two hours to inactivate viral contaminants. The heat treatment also causes a precipitate to form. . . . the suspension including the precipitate first is homogenized, preferably by sonication, and then the precipitate is separated from the suspension. The suspension then may be stored or used for transfusion.

Further, see Chao at column 4 lines 40-64. This distinction - that in the therapeutic composition and drug product claimed, the "microparticles are separated from the liquid medium into which they had been released - has been inserted into the claims to remove all doubt that the supernatant has not been added back to the composition.

For all the foregoing reasons, the claims are not anticipated by Chao, so that the rejection should be withdrawn.

**3. The Claims Are Not Obvious**

Claims 17-23 are rejected under 35 U.S.C. §103(a) as obvious over Knighton taken with Chao, United States Patent No. 5,552,290 by Michelson et al. ("Michelson") and United States Patent No. 5,697,980 by Otani et al. ("Otani"). The Examiner states:

> It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add various carriers, fillings, biodegradable materials and devices including titanium, apatite and organic polymers to modify the drug compositions taught by [Knighton] and/or [Chao] as suggested by [Knighton] with a reasonable expectation of success in wound healing because the claimed carriers and materials are known and used for making artificial filling, carriers and medical devices as adequately demonstrated by [Otani]. One of skill in the art would have been motivated to adjust carrier compositions of [Knighton] and of [Chao] with regard to a mode of administration for the expected benefits in wound healing and/or bleeding reduction as provided by microparticles derived from blood platelets. The knowledge about the use of various platelet activating agents for making and collecting the platelet derived microparticles is available in the prior art as adequately demonstrated by [Michelson].

In the Response to Arguments section of the Official Action, the Examiner states:

> [A]pplicants argue that there is no suggestion, motivation and/or reasonable expectation of success for the combined references because platelet activation elicits a variety of physiological responses as supported by evidentiary reference by Gemmeli et al. (response pages 9-10). However, final nature of "microparticles" obtained from the activated platelet is not recited for the applicants' product as claimed and as disclosed. The references cited in the office action are in the same field of endeavor such as drug compositions intended for wound healing and comprising the platelet-derived microparticles and they seek to solve the same problems as the instant application and claims such as provide for the wound healing and comprising the platelet-derived microparticles, and one of skill in the art is free to select components available in the prior art [citation].

In response, Applicants assert that the "Response to Argument" provided by the Examiner demonstrates that the Examiner has not at all considered the main thrust of Applicants' position, namely "that the cited references utilize the supernatant, whereas the present invention

separates the microparticles *from* the supernatant and does not use the supernatant." Instead, the "Response to Argument" addresses only a portion of argumentation that was applied to Chao. The Examiner has ignored Applicants' statement:

> Applicants continue to dispute that Chao teaches activated platelets, for reasons set forth above, but even if, for the sake of argument, Chao teaches activation, the fact that Chao uses the supernatant does not render obvious the presently claimed invention, which does not use the supernatant.

Therefore, as stated with regard to the 102(b) rejections, Applicants have amended the claims to remove all doubt and to require that, in the claimed compositions, the microparticles remain "separated from the liquid medium into which they had been released." This substantial difference - where the claimed invention discards an important component required by the prior art - distinguishes the claimed invention over the cited references which, taken singly or in combination, cannot create a reasonable expectation of success in practicing the invention. Accordingly, the rejection should be withdrawn.

**CONCLUSION**

For all the foregoing reasons, the rejections should be removed and the claims should be allowed to issue.

Respectfully submitted,

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